# The association between active proliferative lupus nephritis during pregnancy and small for gestational age newborns

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## Abstract

### Objective

*To analyse maternal variables associated with occurrence of small for gestational age (SGA) newborns in pregnancies of women with systemic lupus erythematosus (SLE), considering clinical and laboratory characteristics prior to conception, during gestation and comorbidities.*

### Methods

*Retrospective cohort study with SLE pregnant patients and singleton deliveries after 22 weeks. SGA newborn was defined as birth weight below 10$^{th}$ percentile and SLE activity at conception and during gestation was measured using the SLE Pregnancy Disease Activity Index (SLEPDAI). Univariate analysis was employed to evaluate individual influence of demographic and clinical variables on the SGA newborn outcome, while variables with p<0.20 were included in multivariate regression.*

### Results

*Among 151 pregnancies, 28 (18.5%) had SGA newborns. History of proliferative nephritis (RR=3.84, CI 1.63–9.3) and positivity for anti-RNP and anti-Sm antibodies (RR=2.67, CI 1.11–6.43; 2.78, CI 1.44–5.32) were more frequent in the study group. Active proliferative nephritis at conception (RR=3.29, CI 1.75–6.18) and during gestation (RR=3.63, CI 1.97–6.71), as well as complement C3 consumption (RR=2.70, CI 1.09–6.67) and venous pulse therapy with methylprednisolone (RR=20.3, CI 2.18–190), were also associated with SGA newborns, the latter being independently associated in multivariate regression. Adverse perinatal outcomes, such as stillbirths (4.3 times) and neonatal intensive care unit admissions (3.2 times), were more frequent among SGA infants.*

### Conclusion

*Active proliferative lupus nephritis during pregnancy was associated with SGA newborns, while its treatment with venous pulse therapy with methylprednisolone may play a significant role in this context. Presence of previous proliferative nephritis, SLEPDAI ≥4, C3 consumption and presence of anti-RNP and anti-Sm antibodies were additional variables associated with SGA newborns in this population.*

**Key words**

systemic lupus erythematosus, lupus nephritis, birth weight, small for gestational age

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## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with a broad spectrum of clinical presentation and severity. It primarily affects women at reproductive age and typically presents periods of activity and remission that clearly interferes with gestational outcomes (1). Despite recent advances in therapy and improved survival rates, pregnant women with SLE still have a higher frequency of maternal and foetal morbidity (2, 3), such as utero-placental dysfunction, represented as foetal growth restriction (FGR) during ultrasound evaluation and small for gestational age (SGA) newborns.

Incidence of FGR in pregnancies with SLE is greater than in the general population (5 to 30% *vs*. 7 to 15%) (4, 5), with a perinatal mortality rate 10 times higher than normal foetuses. Those who survive are more prone to neonatal morbidity, delayed neurological development, learning disabilities, behavioural changes, and cerebral palsy (6). In adulthood, there is still an increased risk of arterial hypertension, type 2 diabetes, obesity, atherosclerosis, hypercholesterolaemia, and cardiovascular disease (7, 8).

The present study aimed to analyse maternal variables associated with occurrence of SGA newborns in a cohort of SLE patients followed at a high-risk prenatal clinic for rheumatic and autoimmune diseases.

## Materials and methods

This is a retrospective cohort study with analysis of clinical and laboratory variables in pregnant SLE patients, followed in Pedro Ernesto University Hospital (Rio de Janeiro, Brazil). All patients classified with SLE according to the American College of Rheumatology (ACR) criteria (9), presenting singleton pregnancies and deliveries after 22 weeks of gestation between January 2011 and December 2016 were included. Besides SLE classification criteria, other inclusion criteria were: available data about the disease state at conception and during gestation (activity score); gestational age at delivery; and newborn's birth weight and gender. Patients with less than four SLE classification criteria (n=10), pregnancies whose foetuses presented congenital malformations (n=2), aneuploidies (n=2), miscarriages (n=8) and multiple pregnancies (n=2) were excluded.

SLE activity at conception and during gestation was measured with the Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) (10, 11), as well as steroids and/or immunosuppressive adjustments due to active disease. Patients were classified with active SLE if SLEPDAI was ≥4 and inactive disease was defined as SLEPDAI <4 (12).

Previous lupus nephritis (LN) was confirmed when the patient had biopsy proven classes II, III, IV and V LN, according to the ISN/RPS 2003 classification (13). For those patients without biopsy, LN was established by the presence of proteinuria greater than or equal to 500 mg/24h or urinary protein/creatinine ratio higher than 0.5. In those patients, histologic classification was made by clinical inference according to previously published criteria (1).

Currently accepted definition of FGR is a foetus with estimated weight below the 10$^{th}$ percentile for gestational age during ultrasound evaluation (7, 14, and 15), being considered as severe those classified below the 3$^{rd}$ percentile. The clinical confirmation of a growth restricted foetus is a SGA newborn, defined as birth weight below the 10$^{th}$ percentile (16). The International Foetal and Newborn Growth Consortium for the 21$^{st}$ Century (INTERGROWTH-21) growth curves were used to classify birth weight (17, 18). In four cases of births at 22 and 23 weeks, the Fenton curve was used to classify growth, since the INTERGROWTH-21 curves start at 24 weeks (19).

Univariate analysis was used to evaluate individual influence of demographic and clinical variables on the SGA newborn outcome. In the multivariate analysis, independent predictors were selected by stepwise forward selection method. Through univariate analysis, explanatory variables with $p<0.20$ were included in the multivariate regression.

Comparison between the groups with SGA and non-SGA newborns was analysed by Student's t-test (parametric) or

**Table I**. Demographic, clinical and immunological features of patients according to SGA NB outcome.

| Variable | SGA (n=28) | | non-SGA (n=123) | | RR | CI 95% | *p*-value |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | | | |
| Maternal age at delivery (years) mean ± SD | 28.3 ± 7.1 | | 28.5 ± 5.7 | | 1.00 | 0.93 - 1.07 | 0.90 |
| Duration of SLE (years) median (Q1 - Q3) | 6.5 (3-10) | | 7 (3-11) | | 0.97 | 0.89 - 1.05 | 0.45 |
| Permanent damage by SDI ≥1 - n=38 | 11 | 39.3 | 27 | 22 | 2.30 | 0.96 - 5.49 | 0.061 |
| SLE involvement before pregnancy | | | | | | | |
| Cutaneous | 23 | 82.1 | 111 | 90.2 | 0.50 | 0.16 - 1.55 | 0.23 |
| Articular | 25 | 89.3 | 111 | 90.2 | 0.90 | 0.24 - 3.43 | 0.88 |
| Haematological | 14 | 50 | 77 | 62.6 | 0.60 | 0.26 - 1.36 | 0.22 |
| Neuropsychiatric | 7 | 25 | 24 | 19.5 | 1.37 | 0.52 - 3.61 | 0.52 |
| Serositis | 9 | 2.1 | 44 | 35.8 | 0.85 | 0.35 - 2.04 | 0.72 |
| Nephritis | 18 | 64.3 | 46 | 37.4 | 2.99 | 1.27 - 7.28 | 0.005 |
| Proliferative (classes III/IV) | 17 | 94.4 | 35 | 28.4 | 3.84 | 1.63 - 9.30 | 0.0009 |
| Non-proliferative (classes II/V) | 1 | 5.6 | 11 | 8.9 | 0.37 | 0.01 - 2.37 | 0.19 |
| Immunological profile | | | | | | | |
| Anti-RNP | 11 | 39.3 | 24 | 19.5 | 2.67 | 1.11 - 6.43 | 0.029 |
| Anti-Sm | 9 | 32.1 | 13 | 10.5 | 2.78 | 1.44 - 5.32 | 0.004 |
| Anti-Ro/SSA | 12 | 42.9 | 60 | 48.8 | 0.79 | 0.34 - 1.80 | 0.57 |
| Anti-La/SSB | 2 | 7.1 | 13 | 10.6 | 0.65 | 0.14 - 3.06 | 0.59 |
| Antiphospholipid syndrome | 3 | 10.7 | 16 | 13 | 0.80 | 0.22 - 2.97 | 0.74 |
| Positive aPL* without APS | 2 | 7.1 | 11 | 8.9 | 0.78 | 0.11 - 3.40 | 0.40 |

Categorical data were expressed by frequency (n) and percentage (%) and numerical data by mean ± standard deviation (SD) or median and interquartile range (Q1 - Q3). Relative risk (RR) and its confidence interval of 95% (CI 95%) according to individual binary logistic regression. SLE: systemic lupus erythematosus. SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index *aPL: antiphospolipid antibodies.

Mann-Whitney test (non-parametric) for numerical data, and by the chi-square test ($\chi^2$) or Fisher's exact test for categorical data. Statistical analysis was performed using statistical software SAS® System, v. 6.11 (SAS Institute, Inc., Cary, North Carolina). The institution's ethics committee review board approved the study.

## Results

A total of 151 gestations in 139 SLE patients were analysed. Twenty-eight pregnancies resulted in SGA newborns (18.5%) and 123 were classified as non-SGA newborns. Among the 28 SGA infants, 19 (67.9%) were below the 3rd percentile and/or had abnormalities in foetal Doppler velocimetry, which may represent greater severity and worse prognosis. All these severe cases were already identified as FGR by routine ultrasound and the positive predictive value for ultrasound FGR diagnosis was 90.5% (19/21), with a negative predictive value of 93% (121/130).

Demographic and clinical variables of included patients are described in Table I. Considering the total sample, mean maternal age at delivery was 28.4±6.0 years, with no difference between SGA and non-SGA groups. There was also no statistical difference when mean gestational age at delivery of excluded patients (29.2±6.7) was compared to the whole sample or even to the groups included in the analysis. Fourteen patients with SGA newborns were nulliparous (14/28, 50%), a similar proportion to the patients that had adequate for gestational age newborns (58/123, 47.1%) ($p$=0.39).

Regarding clinical and laboratorial manifestations that occurred during the whole course of disease, 43% (64/151) had a past history of nephritis (SGA 18/28, non-SGA 46/123) and 20.5% had neuropsychiatric manifestation. In those patients with history of nephritis, mean serum creatinine levels were within normal range but statistically higher in the SGA group (0.89±0.31 excluding one patient on dialysis *vs*. 0.64±0.24 on non-SGA group). Twenty-nine (19.2%) patients had chronic hypertension, 19 (12.6%) patients had antiphospholipid syndrome (APS) and 13 (8.6%) only had positive antiphospholipid antibodies (aPL) without APS. Low serum complements (C3 and C4) were identified in 32.4% of the patients. Forty-three patients (28.5%) had active lupus at conception. Twenty-one (49%) of these had active lupus nephritis, with nineteen being classified with proliferative nephritis (classes III/IV). Five patients were submitted to methylprednisolone intravenous pulse therapy during pregnancy, all due to active nephritis classes III or IV. Variables related to LN (active nephritis at conception and during pregnancy, pulse therapy), increased SLEPDAI at the end of gestation, low C3, positivity for anti-RNP and anti-Sm were significantly associated with the main outcome (Table II). There was no statistically significant difference between groups for other clinical manifestations, including non-renal activity, active mesangial and membranous nephritis (classes II and V), immunological features and co-morbidities, as well as for other treatments besides pulse therapy during pregnancy (Table III).

Neonatal intensive care unit (ICU) admission (50% *vs*. 15.4%, $p$<0.0001) and stillbirths (14.3% *vs*. 3.3%, $p$=0.039) were more frequent among SGA infants (Table IV). All stillbirths in the SGA group had severe growth restriction (birth weight below 3rd percentile), with a median gestational age at intrauterine death of 26.5 weeks and mean birth weight of 763.5±580g. In all SGA stillbirths, the mother had active nephritis at conception and half of them (2/4) received intravenous pulse therapy with methylprednisolone during pregnancy.

Perinatal mortality was 7.3% (8 intrauterine deaths and 3 neonatal deaths), with a survival rate of 92.7% of new-

**Table II**. Disease activity by clinical judgment and serological markers at the beginning and at the end of gestation according to SGA NB outcome.

| Variable | SGA (n=28) | | non-SGA (n=123) | | RR | CI 95% | | *p*-value |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | | | | |
| Active SLE at conception | 10 | 35.7 | 33 | 26.8 | 1.52 | 0.63 | - 3.62 | 0.35 |
| Non-renal activity | 5 | 17.8 | 27 | 21.9 | 0.80 | 0.33 | - 1.95 | 0.42 |
| Active nephritis at conception | 9 | 32.1 | 12 | 9.75 | 2.93 | 1.53 | - 5.59 | 0.004 |
| *Proliferative (classes III/IV)* | 9 | 100 | 10 | 83.3 | 3.29 | 1.75 | - 6.18 | 0.001 |
| *Non-proliferative (classes II/V)* | 0 | 0 | 2 | 16.7 | 0 | 0 | - 15.39 | 0.33 |
| Active SLE during gestation | 10 | 35.7 | 34 | 27.6 | 1.35 | 0.67 | - 2.69 | 0.26 |
| Non-renal activity | 4 | 14.3 | 27 | 21.9 | 0.64 | 0.24 | - 1.72 | 0.26 |
| Active nephritis during gestation | 10 | 35.7 | 14 | 11.4 | 2.94 | 1.44 | - 5.56 | 0.003 |
| *Proliferative (classes III/IV)* | 10 | 100 | 10 | 71.5 | 3.63 | 1.97 | - 6.71 | 0.0003 |
| *Non-proliferative (classes II/V)* | 0 | 0 | 4 | 28.5 | 0 | 0 | - 54.5 | 0.21 |
| SLEPDAI at the beginning of gestation (points) - median (Q1-Q3) | 2 (0-6) | | 1 (0-4) | | 1.09 | 0.99 | - 1.19 | 0.088 |
| Anti-DNA | 10 | 35.7 | 26 | 21.1 | 2.07 | 0.85 | - 5.03 | 0.10 |
| C3 consumption | 7 | 25.0 | 22 | 17.9 | 1.53 | 0.58 | - 4.04 | 0.39 |
| C4 consumption | 6 | 21.4 | 11 | 8.9 | 0.36 | 0.12 | - 1.08 | 0.067 |
| SLEPDAI at the end of gestation (points) - median (Q1-Q3) | 4 (0 - 7.5) | | 1 (0 - 3) | | 1.10 | 1.01 | - 1.20 | 0.026 |
| Anti-DNA | 9 | 32.1 | 25 | 20.3 | 1.86 | 0.75 | - 4.60 | 0.18 |
| C3 consumption | 10 | 35.7 | 21 | 17.1 | 2.70 | 1.09 | - 6.67 | 0.031 |
| C4 consumption | 6 | 21.4 | 12 | 9.8 | 2.52 | 0.86 | - 7.44 | 0.094 |

Data were expressed by frequency (n) and percentage (%) for categorical data. Relative risk (RR) and its confidence interval of 95% (CI 95%) according to individual binary logistic regression.
SLE: systemic lupus erythematosus; SLEPDAI: SLE Pregnancy Disease Activity Index.

**Table III**. Treatment during pregnancy according to SGA NB outcome.

| Variable | SGA (n=28) | | non-SGA (n=123) | | RR | CI 95% | | *p*-value |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | | | | |
| Methylprednisolone intravenous pulse therapy | 4 | 14.3 | 1 | 0.81 | 20.3 | 2.18 | - 190 | 0.008 |
| Oral prednisone | 19 | 67.9 | 77 | 62.6 | 1.26 | 0.53 | - 3.02 | 0.60 |
| Azathioprine | 14 | 50 | 54 | 43.9 | 1.28 | 0.56 | - 2.91 | 0.56 |
| Hydroxychloroquine | 27 | 96.4 | 121 | 98.4 | 0.45 | 0.04 | - 5.10 | 0.52 |
| Low dose aspirin | 24 | 85.7 | 106 | 86.2 | 0.96 | 0.30 | - 3.12 | 0.95 |
| Heparin | 5 | 17.9 | 20 | 16.3 | 1.12 | 0.38 | - 3.29 | 0.84 |

Data were expressed by frequency (n) and percentage (%) for categorical data. Relative risk (RR) and its confidence interval of 95% (CI 95%) according to individual binary logistic regression.

borns in the total sample. Survival among SGA newborns was 84% and in the non-SGA newborns was 93.2%, with no significant difference between the groups ($p$=0.10).

All statistically significant variables, previously mentioned in univariate analysis, were selected for multivariate analysis by logistic regression. Administration of intravenous pulse therapy with methylprednisolone for active proliferative nephritis during pregnancy was found as an independent risk factor for the SGA newborn outcome (RR=24.5, 95% CI 2.1–283, $p$=0.010).

## Discussion

In this study, the rate of SGA newborns was 18.5%. This is in accordance with published rates for patients with SLE (5 to 30%) and higher than that observed in general population (7 to 15%) (4, 5, 7). The presence of active lupus at conception is associated with worse maternal and foetal prognosis (20), and can be a predictor of perpetuation of activity throughout gestation. Patients who have active SLE at conception may have up to twice as much risk of activity during pregnancy and 3.5 times higher risk of FGR (21-23).

In our cohort, almost one third of patients who had SGA newborns presented active disease at conception and 35% had active proliferative nephritis during pregnancy, while this frequency was 10% and 11%, respectively, in patients with non-SGA newborns. The local adherence to lupus treatment and contraceptive methods in Brazil is low and discontinuation of all medications due to potential risk of teratogenicity is frequent, which results in higher frequency of activity at conception (25). It is important to note that sixty-five percent of pregnancies in Brazil are not planned (26).

Considering pregnant women with active nephritis at conception, 81% (17/21) remained with active disease during pregnancy, demonstrating an activity perpetuation rate higher than that previously described in the literature (17, 27, 29). Seventeen of the 18 patients with a history of nephritis and SGA newborns had proliferative LN (classes III and IV), and four of them required intravenous pulse therapy. Proliferative LN has a more aggressive behaviour, is associated with a higher risk of reactivation in pregnancy and a greater frequency of activity at conception due to the lower rates of complete

**Table IV.** Characteristics of birth and newborn according to SGA classification.

| Variable | SGA (n=28) | | non-SGA (n=123) | | *p*-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Gestational age at delivery (weeks) | | | | | |
| median (Q1 - Q3) | 36.5 (3-38) | | 38 (3-39) | | 0.05 |
| Preterm birth | 10 | 41.6 | 38 | 31.9 | 0.17 |
| Birth weight (g) mean ± SD | 1831 ± 687 | | 2794 ± 741 | | <0.0001 |
| Neonatal ICU admission | 14 | 50 | 19 | 15.4 | <0.0001 |
| Stillbirth | 4 | 14.3 | 4 | 3.3 | 0.039 |
| Neonatal death | 0 | - | 3 | 2.6 | 0.31 |

Categorical data were expressed by frequency (n) and percentage (%). Numerical data were expressed by mean ± SD (standard deviation) or median and interquartile range. ICU: intensive care unit.

remission (1, 24 and 30). The results of the current study are in consonance our previously publication, that adverse foetal and neonatal outcomes appear to be more related to active proliferative lupus nephritis rather than non-renal disease or even different classes of renal involvement (classes II and V) (24). Usual acute treatment for active SLE is corticosteroids and, during pregnancy, high doses may influence placental angiogenesis. Glucocorticoids can affect the expression of VEGF receptor and also reduce the production of TNF and interleukin 6, placental cytokines that have a regulatory effect on angiogenesis. Disturbances in the development and functioning of the villous vascular system generate reduction of uteroplacental blood flow and contribute to the pathogenesis of foetal growth restriction (31).

SLE activity measured by SLEPDAI score at the end of gestation was also significantly higher in the SGA group (32). Scales of disease activity during pregnancy are not often used in clinical practice, but the observed association suggests that they may be useful in identifying pregnant women at increased risk of developing FGR.

Complement C3 consumption can be related to the high frequency of activity during gestation in the sample, around 30%. Of the 31 patients with C3 consumption at the end of gestation, 17 had active disease (54.8%). There are publications that correlate hypocomplementaemia during gestation with other adverse obstetric outcomes, such as pregnancy loss and preterm birth, regardless of SLE activity (33). In the same way, a prospective study with 47 patients with APS described hypocomplementaemia as an independent predictor of lower birth weight and lower gestational age at delivery (34).

Anti-RNP and anti-Sm antibodies are highly specific for the diagnosis of SLE and may be present in about 30% of patients. Some authors have described that Anti-RNP antibodies, especially when associated to anti-Sm, are more frequent in patients with lupus nephritis, which can justify the higher frequency of these antibodies in the SGA group (35). However, this association between anti-RNP and anti-Sm antibodies and SGA newborns, found in our study, is not described in the literature and deserves further investigation.

Recent reports have demonstrated that hydroxychloroquine may reduce the incidence of FGR and prematurity in patients with SLE (36), however not all publications have reached the same conclusion (37). The universal use of hydroxychloroquine medication in the studied population (98% of the cohort was using the medication at the end of gestation) did not allow it to be used it as a variable of discrimination between the groups. Similarly, the administration of low dose aspirin to pregnant women with high risk for pre-eclampsia, perinatal death and SGA newborns significantly decreases the occurrence of these events when started before 16 weeks (38, 39, 40). Despite the use of aspirin by more than 85% of patients during gestation, the frequency of FGR was still high in this study.

When FGR is identified in antenatal screening, foetal well-being surveillance increases and delivery is scheduled at the most opportune moment, balancing the risk of intrauterine death with the morbidity and mortality of prematurity (41). In our study, all severe cases (birth weight below 3rd percentile and/or Doppler abnormalities) were accurately identified during routine ultrasound screening, performed monthly after 24 weeks in our center. This diagnostic accuracy for FRG is better when foetal biometry evaluation is associated with the analysis of uterine and foetus-placental circulation by Doppler velocimetry, which was used in all cases (19, 21). The evaluation of anti-angiogenic and angiogenic cytokines, such as sFlt-1 and PIGF, may also help identify women at higher risk of placenta-mediated complications like FGR, as they are strongly associated with Doppler velocimetry changes and histological signs of placental hypoperfusion (21, 22, 42).

Regarding foetal death, placenta-mediated obstetric complications are the leading cause in patients with SLE (42). Intrauterine deaths in women with SLE occur earlier than in controls (median 29 weeks in patients with SLE versus 35 weeks in healthy patients) and are more frequent in cases of severe FGR (below the 3rd percentile) or altered flow at foetal Doppler velocimetry (43, 44). In this study, foetal deaths in patients with FGR were even earlier (26 weeks), with all SGA stillborn below the 3rd percentile and 75% of them presented abnormalities in Doppler velocimetry. Neonatal deaths and prematurity were not statistically different between groups in this study.

The retrospective analysis and the single center characteristic are limitations of this study. Although it is a cohort of 151 pregnancies in 139 women with SLE, some variables had a small number of events, which lead to high relative risks and wide confidence intervals. On the other hand, all patients were evaluated by both obstetricians and rheumatologists with experience in pregnant patients with SLE, which may increase the accuracy of reported diagnosis.

In conclusion, this study demonstrates that active proliferative nephritis during pregnancy was associated with SGA newborns, while its treatment with intravenous pulse therapy with methylprednisolone may play a significant

role in this context. Presence of previous proliferative nephritis, SLEPDAI ≥4, complement C3 consumption, presence of anti-RNP and anti-Sm antibodies were additional variables associated with SGA newborns in this population. Regular screening with ultrasound and Doppler velocimetry may identify foetuses at higher risks for adverse perinatal events.

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